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EXAMINER	
PORTNER, VIRGINIA ALLEN	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/462,682	Applicant(s) Fitzgerald
	Examiner Portner	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 3, 2001* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above, claim(s) *4-6, 11, 14-23, 26, 28, 31, 32, 34-36, and 39-43* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 7-10, 12, 13, 24, 25, 27, 29, 30, 33, 37, and 38* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *1-43* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Claims 1-43 are pending.

Claims 4-6, 11, 14-15, 16-18 (claims 16-18 recite specific species of invention not elected), 19-23, 26 (species not elected), 28, 31, 32, 34-36, 39 and 40-43 are withdrawn from further consideration as drawn to non-elected inventions.

Claims 1-3, 7-10, 12-13, 24-25, 27, 29-30, 33, 37-38 are under consideration.

SEQUENCE COMPLIANCE

1. The instant Application is now in sequence compliance.

Information Disclosure Statement

2. The information disclosure statement filed April 28, 2001 has been considered as to the merits.

Election/Restrictions

3. Applicant's election with traverse of Group I, species PE is the cell recognition domain (claim 3) and the non-native epitope is contained in the cysteine-cysteine loop containing a non-native eptiope (claim 9) in Paper No. 10, dated October 3, 2001 is acknowledged. The traversal is on the ground(s) that Applicant disagrees that "all species are distinct from each other" because they ~~the~~ share a common structure.

4. This is not found persuasive because the species are distinct when the species define an independent and distinct invention, wherein a different structure and function of a non-native eptiope would define an independent and distinct species. For example, SEQ ID No 3 and SEQ ID NO 4 would induce antibodies with different binding specificities based upon differences in amino acid structure, and would evidence different binding specificities thereto. Non-elected species are herein withdrawn. The species lack the same or corresponding special technical features for the following reasons: each cell recognition domain, differs in both structure, function and biological effect, specifically the type of immune response induced. Each cell recognition domain will interact with a different type of receptor and will induce a different type of immune response. Each non-native epitope also differs in structure, function and biological effect. The different specificities of immune responses stimulated is directly correlated with the different sizes (5 to 1500 amino acids) and structures (linear or V3 loop apex). Thus each different species defines an independent and distinct invention, that is not linked by a shared special technical feature defined in claim1, as Pastan et al (5,328,984) describes this feature.

The requirement is still deemed proper and is therefore made FINAL.

5. Claims 4-6, 11, 14, 15-18 (claims 16-18 recite specific species of invention not elected), 19-23, 26(species not elected),28, 31,32, 34-36, 39 and 40-43 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups II, III and

non-elected species of Group I, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

6. Elected Group I, claim(s) 1-3, 7-10, 24-25, 27, 29-30, 33 and 37-38 are under consideration drawn to chimeric immunogens that comprise non-toxic Pseudomonas exotoxin A, wherein:

7. the cell recognition domain is Ia of PE (claims 3, elected species),

8. the translocation domain is PE domain II

9. the ER domain comprises an ER retention sequence.

10. the non-native epitope contained within a cysteine-cysteine loop (claim 9 elected species) and methods of stimulating an immune response.

Claim Rejections - 35 U.S.C. § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 27, 29-30, 33, 37-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the preparation and administration of an immunogenic chimeric PE-like molecule that comprises a non-native epitope, does not reasonably provide enablement for the use of the immunogen for stimulation of a protective immune response for

the prophylactic or therapeutic treatment of any disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed invention is directed to vaccine compositions and methods of eliciting an preventative or therapeutic immune response through administering the vaccine composition that comprises a chimeric immunogen containing a non-native epitope.

The specification fails to teach how to formulate and use the claimed vaccines. The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity to prevent infection or disease induction or to treat pre-existing infection and in this case the antigen would be an epitope. The specification teaches that the claimed epitopes will immunoreact with antibodies and could stimulate an immune response, but the specification does not provide substantive evidence that the claimed vaccines are capable of inducing protective immunity to any non-native epitope of any size of 5 amino acids up to 1500 amino acids. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of treating or preventing infection. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced.

The ability to reasonably predict the capacity of a single bacterial immunogen to induce protective immunity from in vitro antibody reactivity studies is problematic. Ellis exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the

identification of the at protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies"(page 572, second full paragraph). Unfortunately, the art is replete with instances where even well characterized antigens that induce an in vitro neutralizing antibody response fail to elicit in vivo protective immunity. See Boslego et al. wherein a single gonococcal pillin protein fails to elicit protective immunity even though a high level of serum antibody response is induced (page 212, bottom of column 2).

No teaching or guidance as to what characteristics and amino acid seqeunces must be present in any epitope to insure that it will induce a protective immune response has been provided. No examples are shown that provide the missing information how to make and use any epitope as a vaccine composition. Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful vaccine without the prior demonstration of vaccine efficacy.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1, 2, 7-10, 12, 24-25, 27, 30, 33 and 37-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1(section 2) recites the phrase "substantially identical to a sequence of PE domain II". How does the sequence differ from the sequence of PE domain II? What changes have been made to the sequence and where? Section (2) also recites the phrase "sufficient to effect translocation to a cell cytosol". What is the sequence required to effect translocation to a cell cytosol? How does the sequence that is sufficient differ from native PE?

Claim 1(section 3) recites the phrase "encodes a non-native epitope". What is the non-native epitope, non-native to? While it is clear that the chimeric immunogen comprises a non-native epitope, is this epitope in addition to the cell recognition domain set forth in section (1) and the endoplasmic reticulum retention domain of section (3)? The cell recognition and the endoplasmic reticulum retention domains are not limited to domains of PE, but can be any cell recognition and the endoplasmic reticulum retention sequences from a non-native source. Are the cell recognition domain, the endoplasmic reticulum retention domains and the non-native epitope one in the same component, and the phrase "encodes a non-native epitope" a functional limitation of the cell recognition domain in view of the fact that the cell recognition and the endoplasmic reticulum retention domains, as now claimed, are not limited to the domains of PE?

Claim 1 is directed to "A non-toxic Pseudomonas exotoxin A-like chimeric immunogen". How is the immunogen like PE, if it only comprises an amino acid sequence that is substantially similar to that of the PE domain II? What makes the immunogen non-toxic? Domain II of PE does not mediate toxicity of the native molecule? Domains (1), (3) and (4) are not limited to amino acid sequences of PE, and domain (2) is defined to be substantially identical to a sequence

of PE domain II for translocation. The four sections of the claim need not evidence the identical sequence of PE, but must only be functionally similar to the native molecule of PE and be substantially similar to domain II translocation portion. What is the structure of the claimed chimeric immunogen? What are the claimed amino acid sequences of between 10 and 1500 amino acids (section 1) and between 5 and 1500 amino acids of section (3)? The claimed genus of molecules range in size from about 104 amino acids (10 + 85 + 5 + 4=104) to about 3325 amino acids in length (1500 + 111 + 1500 + 214 =3325). What are the claimed sequences with the recited functions?

Claims 1, 24, 27, 33 all recite epitopes of up to 1500 amino acids. Epitopes are defined by the antibody that bind thereto. What antibody can bind to an epitope that is 1500 amino acids? Clarification of the size and nature of the non-native epitope and the domain that contains the epitope is requested.

Claim 2 recites the phrase "having the amino acid sequence of PE ΔE553". This phrase lacks antecedent basis in claim 1 from which it depends. The sequence of claim 1 has not been so claimed as to comprise domain 1b of PE, nor has it been defined to have the amino acid E553. Which domain of the molecule of claim 1 is domain 1b ? The claimed chimeric immunogen need only have 104 amino acids in it, and the molecule of claim 2 is directed to the deletion of amino acid 553, which is not required to be in the molecule of claim 1. How many amino acids does the molecule of claim 2 have? Clarification of where domain 1b corresponds to in claim 1, relative to the claim limitations recited in claim 2 is requested.

Claim 7 is vague and indefinite in the absence of a reference sequence (SEQ ID NO) in light of the fact that the claimed immunogen is not limited to PE, the claimed domain II of claim 1 is not identical to the sequence of PE, but is substantially identical to the translocation portion of PE domain II, and what changes have been made are not distinctly set forth.

Claim 8 sets forth that the translocation domain is domain II of PE and depends from claim 1. Claim 1 defines domain II to differ from the sequence of PE domain II and claim 8 defines domain II to be domain II of PE. The language used in the claim is unclear in light of claim 1 defining domain II to not be identical to domain II of PE. Clarification is requested.

Claim 9 recites the phrase "the non-native epitope domain comprises a cysteine-cysteine loop that comprises the non-native epitope". While it is clear that the cysteine-cysteine loop comprises the non-native epitope, is the cysteine-cysteine loop considered to be a part of the non-native domain ? Claim 1 defines the non-native epitope as the domain, while claim 9 defines the domain to contain more than the non-native epitope recited in claim 1, and must include a cysteine-cysteine loop. Claim 9 broadens the scope of claim 1, but defining the non-native epitope domain to comprise more than just the non-native epitope as recited in claim 1. Clarification is requested.

Claim 10 recites the phrase "a non-native epitope inserted between two cysteine residues of domain 1b of PE". Where in the PE-like immunogen of claim 1 is the domain 1b? The phrase "domain 1b" lacks antecedent basis in claim 1. Where are the two cysteine residues of domain 1b in the immunogen of claim 1 which is not defined to have any cysteine residues in it ? How many

amino acids does the non-native epitope domain have, in light of the fact that the 1b domain is defined to have two cysteines and a non-native epitope of any size? The non-native epitope domain is not limited to the size of the non-native epitope of claim 1 because the non-native epitope is not so described by any specific structure, amino acid number, function or known epitope name. Claim 10 broadens the scope of claim 1, in not defining the size of non-native epitope inserted.

Claim 12 recites the phrase "domain III of PE comprising the mutation ΔE553" and depends from claim 1. While it is clear that the domain contains a mutation, clarification of the term "ΔE553" is requested.

15. Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a correlation step that recites the antibodies are produced. The claimed method is not a method of inoculating an animal, but a method of producing antibodies. How does one know that the antibodies were produced to the non-native epitope if the antibodies are not obtained or isolated from the animal?

Claim 25 defines the cysteine-cysteine loop to comprise "no more than about 30 amino acids". While the claim defines an upper limit of about 30, no lower limit is defined, thus broadening the scope of the claim to include epitopes smaller than 5 amino acids. Claim 25 broadens the scope of claim 24 from which it depends in light of no lower limit being recited in the claim. Clarification is requested.

Claim 27 is directed to a vaccine that comprises a non-native epitope domain, but the epitope is not defined as being a protective epitope or even an immunogenic epitope. How can the epitope function to induce a protective immune response if it is not of a size that will induce an immune response and define a protective epitope? What is the amino acid sequence of the epitopes that are protective and would function as a vaccine?

Claim 30 recites the phrase "the immunogen is present is an amount effective to elicit in a human subject an immune response against the non-native epitope". While it is clear that the amount of the immunogen of claim 30 is sufficient to stimulate an immune response, the amount of immunogen is not defined to stimulate a protective immune response as required by the vaccine of claim 27 from which claim 30 depends. Claim 30 broadens the scope of claim 27 by only requiring the stimulation of any type of immune response and not a protective immune response as define through the recitation of the term vaccine. What is the vaccine to, in claim 27, if it not the non-native epitope? If claim 30 requires the dose to be sufficient to stimulate an immune response to the non-native epitope, to what component of the vaccine of claim 27 is the immune response stimulated ? Is the vaccine to domain II, the cell recognition domain or to the retention domain or the non-native epitope ? None of the domains in claim 27 are defined to induce a protective immune response. In view of claim 27 not defining what the vaccine is, claim 30 also does not distinctly claim the invention of a vaccine, especially in light of the dose only requiring the induction of any type of immune response in a human.

Claim 33 is directed to a method of eliciting an immune response against a non-native epitope in a subject. Is the subject an immunocompetent subject? How can an immune response be stimulated if the composition administered is not to a subject able to produce an immune response? Clarification is requested.

Claim 37 recites the phrase "an agent bearing the non-native epitope". What is the agent? The scope of the claim is not limited to the non-native epitope domain containing immunogen of claim 33 and thus broadens the scope of claim 33.

Claim 38 recites the phrase "an agent bearing the non-native epitope". What is the agent? The scope of the claim is not limited to the non-native epitope domain containing immunogen of claim 33 and thus broadens the scope of claim 33.

Claim Rejections - 35 U.S.C. § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Please note: The "subject" recited in claim 33 is being read to include cells to which the immunogen is administered, in light of the claims not requiring the immunogen be administered to an immunocompetent host animal and the vaccine function to cause cell toxicity.

17. Claims 1, 7-8, 12-13, 27, 29-30, 33 (generic claims) and 3 (elected invention), 9-10 (elected invention) are rejected under 35 U.S.C. 102(b) as being anticipated by Pastan et al (US Pat. 5,328,984).

The claimed invention is directed to a non-toxic Pseudomonas exotoxin-A chimeric immunogen, wherein the chimera comprises Domain 1A, Domain II, Domain III, a heterologous non-native epitope containing amino acid sequence and a mutation at glutamic acid amino acid 553, as well as a non-native epitope domain that comprises an epitope between two cysteine residues in domain 1b ~~and~~ which could form a cysteine-cysteine loop.

(Instant claims 1, 3, 7-8, 12-13, 27, 29-30, 33) Pastan et al disclose a non-toxic Pseudomonas exotoxin-A chimeric immunogen, wherein the chimera comprises Domain 1A, Domain II, Domain III, a heterologous non-native epitope containing amino acid sequence and a mutation at glutamic acid amino acid 553 (see Figure 2, PEΔ553-BAR, wherein BAR is a 110 amino acid sequence (col. 9, lines 5-7; col. 11, lines 18-20). The chimeric immunogen was purified and combined with phosphate buffered saline, 20mM Tris pH7.4 with 1mM EDTA, 250 mM NaCl or in phosphate buffered saline with 0.2% human serum albumin (see col. 7, line 63, 65-66; col.8, lines 1-2, or 21-22).

(Claims 1,7-10, 13, 27, 29-30, 33) Pastan et al disclose a chimeric immunogen with reduced toxicity (see Figure 8, pWD150 and pWD163) and comprise a cell recognition domain (TGFα), a cell translocation domain (domain II), a ER retention sequence (domain III) and an insertion of a non-native epitope between two cysteines in domain 1b. Two non-native epitopes that contained two cysteines were utilized in the formulation of chimeric immunogens, one being SEQ ID NO 2 for somatostatin-14, wherein the cysteines would be capable of forming a cysteine-cysteine loop (see col. 3, lines 7-10; col. 12, lines 15-18; col. 12, lines 44-52) and the other being SEQ ID No. 4, both of which evidenced less toxicity that the native PE (see Figure 8, col. 12, line 20).

The reference teaches Domain 1b as being a site for the efficient insertion of specific peptides, polypeptides, proteins, enzymes, single chain antibodies to insure the insertion of these non-native epitopes into the cell cytoplasm of the targeted cell (see col. 12, lines 44-52), wherein the PE would be non-toxic (without ADP ribosylating activity (col. 12, lines 48-49), would contain domain II and III, as well as a cell recognition domain (col. 12, lines 1-30).

Inherently the reference anticipates the now claimed invention.

Claim Rejections - 35 U.S.C. § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pastan et al (US Pat. 5,328,984) as applied to claims 1, 3, 7-10, 12-13, 27, 29-30, 33 above.

The claimed invention is directed to a method of producing antibodies in an animal and a method of eliciting an immune response in a subject through the inoculation of an animal with the non-toxic PE chimeric immunogen, wherein the immunogen [redacted] comprises a cell recognition domain, a translocation domain, a non-native epitope inserted into the 1b domain between two cysteines and can form a cysteine-cysteine loop and an endoplasmic reticulum retention domain. (Instant Claim 2) See discussion of Pastan et al ('984)above. Pastan et al ('984) disclose a chimeric PE immunogen that is non-toxic in an analogous art for the purpose of delivering non-native epitopes contained in a non-toxic PE to the cytosol of target cells through the deletion of E553 and suggests the incorporation of the non-native epitope into domain 1b of the non-toxic PE for the delivery of peptides, polypeptides, proteins, enzymes and antibodies to the cytosol of cells (see col. 12, lines 44-54 and col. 10, lines 1-3), but differs from the instantly claimed invention by failing to show the formulation of the chimeric immunogen suggested.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the immunogen of Pastan et al ('984) to comprise the deletion of E553 as taught and suggested by Pastan et al ('984) because Pastan et al teaches that domain 1b is an efficient way to accomplish the delivery of an desired non-native epitope containing protein,

peptide, polypeptide, single chain antibody or enzyme to the cytoplasm of a cell, wherein the PE immunogen would be without ADP ribosylating activity and Pastan et al teaches that through the deletion of E553, the molecule is rendered inactive with respect to ADP ribosylating activity.

20. Claims 24-25, 27, 33, 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pastan et al (US Pat. 5,328,984) as applied to claims 1-3, 7-10, 12-13, 27, 29-30, 33 immediately above, in view of Pastan (US Pat. 6,074,644).

See discussion of Pastan et al ('984) above. The Pastan et al ('984) teaches the formulation of a chimeric immunogen that comprises PE and a non-native epitope together with a pharmaceutical carrier, but differs from the instantly claimed invention by failing to show the immunogen used in a method that comprises the step of inoculating an animal or the step of administering the composition to a subject, wherein the subject is an animal.

Pastan et al ('644) teach a method that comprises the step of inoculating or administering to a chimeric PE immunogen (see col. 25, line 20; col. 26, line 15) an animal in an analogous art for the purpose of mediating an immune response. One embodiment shown is a chimeric immunogen that ('644) (col. 3, line 20) comprises a non-native epitope (single chain antibody) inserted into the 1b domain (see col. 8, line 34; col. 9, lines 10-11) that can form a cysteine-cysteine loop(col. 3, line 22), and have no more than about 30 amino acids (col. 3, lines 28).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to employ the chimeric immunogen in a method which comprises the step of administering to or

inoculating an animal with the molecule of Pastan et al (''984) because Pastan et al ('984 and '644) both teach the chimeric immunogens that comprise PE with a non-native epitopes inserted in the 1b domain are made for therapeutic or cytotoxic purposes, and Pastan('644) show a method of administering or inoculating an animal realized therapeutic effect in light of the cell recognition component providing cell specific binding capabilities, and Pastan et al ('984) teaches that non-toxic PE chimeric immunogens evidence fewer side effects to the host and would still be able to be used as a cytotoxic, diagnostic or therapeutic immunogens (abstract, '984).

The person of ordinary skill in the art would have been motivated by the reasonable expectation of success in eliciting an immune response or stimulating the production of antibodies with the non-toxic chimeric PE immunogen of Pastan et al ('984) because the reference provides guidance, and teaching on how to make and use the reagent for the attainment of chimeric immunogens that are targeted against a selected cell types and have the desired attribute of non-toxicity (abstract, figure 2) to the host, but are highly immunogenic in light of the parent molecule being derived from PE, a known superantigen molecule.

In the absence of a showing of unexpected results, Pastan et al ('984) in view of ('644) Pastan et al obviate the now claimed invention.

21. Claims 1-3,7-10, 12-13, 24-25, 27, 29, 30, 33, 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cryz et al (1995) in view Moore (1992) and Pastan et al (US Pat. 5,328,984).

The claimed invention is directed to a chimeric immunogen like PE that comprises a non-native epitope that is inserted into the Ib domain and the non-native epitope is in a cysteine-cysteine loop and a method of eliciting an immune response to the chimeric immunogen.

Cryz et al show the formulation of a chimeric immunogen like PE that comprises a non-native epitope and the non-native epitope is formed by a cysteine-cysteine loop and a method of eliciting an immune response to the chimeric immunogen. The reference teaches that the cysteine-cysteine loop containing epitope is immunogenic and induces neutralizing antibodies to the epitope circularized by the loop. The reference differs from the instantly claimed invention by failing to show the non-native epitope incorporated into the Ib domain of PE and the PE to be non-toxic.

Moore (1992) teaches the importance of retaining cysteine loop structures of synthetic peptides in an analgous art for the purpose of stabilizing peptide immunogens to induce the desired immune response.

Pastan et al teaches the advantage of inserting non-native epitopes anywhere in Ib domain of PE and teaches a non-toxic form of PE for carrying non-native epitopes in an analogous art for the purpose of producing chimeric immunogens of PE for use in cytotoxic, diagnostic and therapeutic methods.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the chimeric immunogen of Cryz et al to be a non-toxic form of PE with an inserted cysteine loop confirmation for the non-native epitope in the Ib domain, in

view of the teaching and guidance of Moore and Pastan et al because Pastan et al teach that through insertion of a non-native epitope of the Ib domain, the non-native epitope can be carried into the cytoplasm of a desired cell and does not interfer with the cell recognition, translocation or endoplasmic reticulum retention components of PE, the chimeric PE immunogen upon inoculation or administration of a non-toxic form of PE to an animal or subject will stimulate an immune response because the non-native epitope has been stabilized through preserving the conformation of the native cysteine-cysteine loop upon insertion to the Ib domain and the animal or subject will evidence fewer negative side effects due to being exposed to a non-toxic form of PE.

In the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated to utilize a "non-native" epitope that is highly immunogenic for the stimulation of antibodies and to maintain the native conformation of the peptide amino acid sequence because Moore teaches through stabilizing the preferred peptide structure the stimulated immune response is specific to the native cysteine-cysteine loop epitope and Cryz et al teach the epitope induces important neutralizing antibodies in native conformation.

Conclusion

22. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

23. Ashorn et al (1990) and Chaudhary et al (2988) are cited to show a CD4-Pseudomonas exotoxin conjugate.

24. Better et al (US Pat. 6,146,631) is cited to show immunotoxins of targeted molecules.

25. Draper (US Pat. 6,086,900) is cited to show Pseudomonas exotoxin conjugates (see claims).

26. EP 439954 A is cited to show chimeric conjugates of Pseudomonas exotoxin.

27. Pastan et al (US Pat. 5,854,044; 5,512,658; 5,980,895) are cited to show various chimeric molecules of Pseudomonas exotoxin A.

28. Wang (US Pat. 6,090,388) is cited to show that peptide immunogens that comprise "a loop structure present on an authentic epitope can be more accurately duplicated on a synthetic peptide by the addition of advantageously placed cysteines (brief summary section).

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.
Vgp
December 14, 2001

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600